Supplementary tables

Table A. PubMed Search Strategy

(Diabetes Mellitus, Type 2[mh] OR ((diabetes[tiab] OR diabetic*[tiab] OR diabetus[tiab]) AND (non insulin depend*[tiab] OR noninsulin depend*[tiab] OR maturity onset*[tiab] OR adult onset*[tiab] OR slow onset*[tiab] OR insulin resistan*[tiab])) OR "diabetes mellitus type 2"[tiab] OR dm2[tiab] OR "dm 2"[tiab] OR t2d*[tiab] OR "dm type 2"[tiab] OR type 2 diabet*[tiab] OR "dm type II"[tiab] OR type two diabet*[tiab] OR type II diabet*[tiab] OR T2 diabet*[tiab] OR T2DM[tiab] OR "dm type II"[tiab] OR diabetolog*[tiab])
AND
(Diet, Carbohydrate-Restricted[mh] OR Diet, Diabetic[mh] OR Dietary Carbohydrates[mh] OR ((carbohydrate restrict*[tiab] OR diabetic[tiab] OR ketogenic[tiab] OR keto[tiab] OR ketone[tiab] OR ketosis[tiab] OR ketotic[tiab] OR low carbohydrate*[tiab] OR "low carb"[tiab] OR "low glycemic"[tiab] OR "low glycaemic"[tiab] OR "low GI"[tiab] OR "south beach"[tiab] OR atkins[tiab] OR dukan[tiab] OR pronokal[tiab] OR PnK[tiab] OR "high protein"[tiab] OR paleo[tiab] OR paleolithic[tiab]) AND (diet[tiab] OR "dietary method"[tiab] OR plan[tiab] OR protocol[tiab])) OR dietary carbohydrate*[tiab] OR carbohydrate quantit*[tiab] OR LCD OR carbohydrate count*[tiab])
AND
(randomized controlled trial[pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])

Table B. Extraction Variables

Citation	First author
	Year of publication
Diet	Diet categorization (e.g. no diet, low CHO, low fat)
	Kcal restricted (y/n - details)?
	Product provided or recommended (y/n - give details)?
	Macronutrient goal (CHO g/day / %, protein (%), lipids (%)
	Supplement (meals/snacks/fruit/etc)
Co-interventions	Co-intervention (y/n - details)?
	Intensity level (behavioral support) 1: High (2 visits per mo x first 3 mo, or food provided); 2: Low (< 2 visit per mo x first 3 mo); 3: no intensity (manual/flyer but no other support)
	Exercise recommended? (y/n – give details)
	Exercise frequency
	Exercise category (0 : none (maintain baseline EX 1 : Low (< 2hrs per week) 2: Moderate (2-4 hrs per week) 3: High (> 4 hrs per week) 99: Unclear
	Exercise type
	Exercise adherence
Study characteristics	Population
	Country
	Randomized total and per group
	Missing participant analysis method (CC, LOCF(BOCF), ITT, other)
	Dietary intake instrument used
	Demographics and prognostic Factors (age, women, Caucasian, smokers, dyslipidemia, metabolic syndrome, CVD history, hypertension, BMI)
	Energy intake
	Treatment duration
	Study duration
	Latest measured endpoint
	Baseline variables (weight, quality of life score, medication use, HbA1c, fasting glucose, TC, LDL, HDL, Triglycerides, inflammatory markers, insulin resistance, SBP, DBP)
Adverse events	Total adverse events reported
	Participants who experienced adverse events
	Total serious adverse events reported
	Participants who experienced serious adverse events
Results	Remission (HbA1c <6.5 and no diabetes medication; HbA1c <6.5 regardless of diabetes medication use)
	Weight loss
	HbA1c
	Fasting glucose
	Adverse events and serious adverse events
	Quality of life measures
	Medication use

	Lipids (TC, LDL, HDL, triglycerides)
	Inflammation markers (e.g. CRP)
	Insulin resistance (e.g. HOMA-IR)
	Dietary intake
	Adherence

Table C. Estimated minimal clinically important differences (MCID)

	Normal	20%*	15%	10%	5%	2.5%	MCID **
Weight	n/a	n/a	n/a	n/a	n/a	n/a	4.4 kg
HbA1c	<5.7%	1.1%	0.9%	0.6%	0.3%	0.1%	0.5%
Fasting glucose	<7 mmol/L	1.40	1.05	0.70	0.35	0.18	1.60 mmol/L
Total cholesterol	<5.2 mmol/L	1.04	0.78	0.52	0.26	0.13	0.26 mmol/L
LDL	2.6 mmol/L	0.52	0.39	0.26	0.13	0.07	0.10 mmol/L
HDL	1 mmol/L	0.20	0.15	0.10	0.05	0.03	0.10 mmol/L
Triglycerides	<1.70 mmol/L	0.34	0.26	0.17	0.09	0.04	0.09 mmol/L
C-Reactive Protein (CRP)	<10 mg/L	2	1.5	1.0	0.5	0.25	0.5 mg/L
HOMA-IR	<1	0.2	0.15	0.1	0.05	0.03	0.05
Homeostasis Model Assessment of Insulin Resistance = HOMA-IR; MCID for quality of life measures were determined by 0.5 SD.[8]							

For very low carbohydrate diets versus active diets or control groups, we used these MCIDs in calculations for optimal information size for the GRADE assessment of imprecision and also in discussing whether the magnitude of a point estimate was clinically meaningful.

***Percentages of the upper bound of normal values.**

****Rationale:**

Weight - Based on generally accepted clinically significant difference of 5% of baseline weight.[1,2] For MCID we used a 5% reduction of the mean baseline weight of a large diabetic cohort (PROVALID).[3]

HbA1c - In general, based on American Diabetes Association and National Institute for Health and Clinical Excellence treatment guidelines, 0.5% HbA1c is considered a clinically significant change.[4]

Fasting glucose - Based on the relationship seen in the baseline data of a diabetic population (ORIGIN trial) between HbA1c levels and fasting glucose. Of those not taking antidiabetic drugs, a 0.5% HbA1c change was associated with 21 mg/dL fasting glucose change. In those taking antidiabetic drugs 0.5% HbA1c change was associated with a 36 mg/dL change.[5] Because our populations included both, we used an average between the two as our MCID for fasting glucose, 28.5 mg/dL and then converted to mmol/L.

Total cholesterol - Based on 5% reduction of upper bound of normal.

LDL and **HDL** - Based on Federal Drug Administration/Health Canada cholesterol-lowering health claims for foods.[6]

Triglycerides - Based on 5% reduction of upper bound of normal.

CRP - Based on Reynolds Risk score 0.5mg/L = 1% change in 10 year CVD risk.[7]

HOMA-IR - Based on 5% reduction of upper bound of normal.

Works Cited

1. Chiavaroli L, Nishi SK, Khan TA, Braunstein CR, Glenn AJ, Mejia SB, et al. Portfolio dietary pattern and cardiovascular disease: A systematic review and meta-analysis of controlled trials. Vol. 61, Progress in Cardiovascular Diseases. 2018;61(1):43-53.
2. Lau DCW, Douketis JD, Morrison KM, Hramiak IM, Sharma AM, Ur E. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children [summary].CMAJ 2007;176(8):S1-S13.
3. Eder S, Leierer J, Kerschbaum J, Rosivall L, Wiecek A, De Zeeuw D, et al. A Prospective Cohort Study in Patients with Type 2 Diabetes Mellitus for Validation of Biomarkers (PROVALID) - Study Design and Baseline Characteristics. Kidney Blood Press Res. 2018 Mar 1;43(1):181–90.

4. ADA. Standards of medical care in diabetes-2009. Vol. 32, Diabetes Care. American Diabetes Association; 2009. p. S13–61.
5. Ramachandran A, Riddle MC, Kabali C, Gerstein HC. Relationship between A1C and fasting plasma glucose in dysglycemia or type 2 diabetes: An analysis of baseline data from the ORIGIN trial. Diabetes Care. 2012;35(4):749–53.
6. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: A report of the American College of cardiology/American Heart Association task force on practice guidelines and the obesity society. Circulation. 2014;129(25 Suppl 2):S102-S138.
7. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: The Reynolds Risk Score. J Am Med Assoc. 2007 Feb 14;297(6):611–9.
8. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life. Med Care. 2003 May;41(5):582–92.

Table D. Subgroup credibility

Subgroup	Outcome	Effect subgroup A	Effect subgroup B	Credibility items
Studies inclusive of participants using insulin vs studies excluding participants using insulin	Diabetes remission	Studies that included participants using insulin. Remission defined by HbA1c <6.5%: RD 0.14 (95% CI 0.03 to 0.25). Remission defined by HbA1c + no diabetic medication: RD -0.00 (95% CI -0.07 to 0.07)	Studies without participants using insulin. Remission defined by HbA1c <6.5%: RD 0.51 (95% CI 0.36 to 0.65). Remission defined by HbA1c + no diabetic medication: RD 0.20 (95% CI 0.03 to 0.38).	4 of 5 criteria met. Credible subgroup. 1. Can chance explain the subgroup difference? No. p=0.02 2. Is the subgroup difference consistent across studies? Yes. I^2 drops to 0% in both groups on analysis. 3. Was the subgroup difference one of a small number of a priori hypotheses in which the direction was accurately prespecified? Probably Yes. We tested 7 *a priori* subgroups with a prespecified direction of effect. 4. Is there a strong pre-existing biological rationale supporting the apparent subgroup effect? Probably Yes. As compared to non-insulin dependent diabetics, patients on insulin are likely to have diabetes of increased severity and may have compromised pancreatic function, impeding diabetes remission. 5. Is the subgroup difference suggested by comparisons within rather than between studies? No. The observed dose-response difference among all studies is based on between study data.
Very Low Carbohydrate Diet (<10% carb) vs 10-26% LCD diets	Weight loss	VLCD: MD -1.05 (95% CI -2.27 to 0.17)	Not VLCD: MD -5.88 (95% CI -9.53 to -2.24)	4 of 5 criteria met. Credible subgroup. 1. Can chance explain the subgroup difference? No. p=0.01 2. Is the subgroup difference consistent across studies? Probably Yes. The majority of VLCD studies had smaller treatment effects. 3. Was the subgroup difference one of a small number of a priori hypotheses in which the direction was accurately prespecified? Probably Yes. We tested 7 *a priori* subgroups with a prespecified direction of effect. 4. Is there a strong pre-existing biological rationale supporting the apparent subgroup effect? Probably Yes. VLCD may be more difficult to sustain. This effect is

				negated when VLCD that were adherent are examined. 5. Is the subgroup difference suggested by comparisons within rather than between studies? No. The observed difference among all studies is based on between study data.
Very Low Carbohydrate Diet – Highly adherent vs less - adherent	Weight loss	Highly adherent VLCD: MD -4.47 (95% CI -8.21 to -0.73)	Less adherent VLCD: MD -0.55 (95% CI -1.76 to 0.66)	4 of 5 criteria met. Credible subgroup. 1. Can chance explain the subgroup difference? Probably no. p=0.05 2. Is the subgroup difference consistent across studies? Probably Yes. The majority of studies with high adherence tended to have larger treatment effects. 3. Was the subgroup difference one of a small number of a priori hypotheses in which the direction was accurately prespecified? Probably Yes. We tested 7 *a priori* subgroups with a prespecified direction of effect. 4. Is there a strong pre-existing biological rationale supporting the apparent subgroup effect? Probably Yes. VLCD have biologic plausibility related to nutritional ketosis.[1] Without strict dietary adherence, though, nutritional ketosis is difficult to maintain potentially negating any additional ketosis-specific weight loss benefits. 5. Is the subgroup difference suggested by comparisons within rather than between studies? No. The observed difference among all studies is based on between study data.

Works cited:

1. Gershuni VM, Yan SL, Medici V. Nutritional Ketosis for Weight Management and Reversal of Metabolic Syndrome. *Curr Nutr Rep*. 2018;7(3):97-106.

Table E. GRADE versus NutriGRADE evidence certainty ratings

Outcome	Point Estimate (95% CI)	GRADE	NutriGRADE
Remission (HbA1c <6.5% 6 months)	RR 1.87 (1.18 to 2.97)	Moderate	Moderate
Remission (HbA1c <6.5% + no diabetes medication 6 months)	RR 1.24 (0.65 to 2.38)	Low	Moderate
Remission (HbA1c <6.5%) 12 months	RR 1.27 (0.99 to 1.64)	Moderate	Moderate
Remission (HbA1c <6.5% + no diabetes medication) 12 months	RR 0.79 (0.36 to 1.73)	Low	Moderate
Weight loss 6 months	MD 3.46 Kg lower (5.25 lower to 1.67 lower)	Moderate	Moderate
Weight loss 12 months	MD 0.29 Kg higher (1.02 higher to 1.6 higher)	Moderate	Moderate
HbA1c 6 months	MD 0.47% lower (0.60 lower to 0.34 lower)	High	High
HbA1c 12 months	MD 0.23% lower (0.46 lower to 0.00)	Moderate	Moderate
Fasting glucose 6 months	MD 0.73 (mmol/L) lower (1.19 lower to 0.27 lower)	Moderate	High
Fasting glucose 12 months	MD 0.06 (mmol/L) higher (0.37 lower to 0.48 higher)	Moderate	Moderate
AE 6 months	RR 1.55 (0.76 to 3.15)	Very low	Low
AE 12 months	RR 0.72 (0.39 to 1.33)	Very low	Low
SAE 6 months	RR 0.79 (0.14 to 4.47)	Low	Moderate
SAE 12 months	RR 0.78 (0.10 to 6.13)	Very low	Low
QoL 6 months	MD -0.97 (-2.68 to 0.73)	Low	Low
QoL 12 months	MD 3.10 (-2.03 to 8.23)	Low	Low
Medication reduction 6 months	RD 0.24 (0.12 to 0.35)	Moderate	Moderate
Medication reduction 12 months	RD 0.33 (0.00 to 0.66)	Low	Low
Total cholesterol 6 months	MD -0.10 (-0.41 to 0.20)	Moderate	Moderate
Total cholesterol 12 months	MD 0.11 (-0.05 to 0.27)	Moderate	Moderate
LDL 6 months	MD 0.02 (-0.09 to 0.12)	High	Moderate
LDL 12 month	MD 0.14 (0.00 to 0.28)	Moderate	Moderate
HDL 6 months	MD 0.06 (0.01 to 0.10)	High	High

HDL 12 months	MD 0.04 (0.00 to 0.08)	High	Moderate
Triglycerides 6 months	MD -0.30 (-0.43 to -0.17)	High	High
Triglycerides 12 months	MD -0.32 (-0.51 to -0.12)	High	Moderate
Insulin resistance 6 months	MD -0.14 (-0.51 to 0.23)	Very low	Low
Insulin resistance 12 months	MD -0.13 (-0.39 to 0.13)	Very low	Low
Inflammation 6 months	MD 0.16 (-0.27 to 0.59)	Moderate	Low
Inflammation 12 months	MD 0.37 (-0.44 to 1.18)	Very low	Low

CI = confidence interval; RR = risk ratio; MD = mean difference; AE = adverse events; SAE = serious adverse events; QoL = quality of life; LDL = low density lipoprotein; HDL = high density lipoprotein

Rating scale on both GRADE and NutriGRADE ranges from “very low” to “high.”